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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,698	09/11/2003	Richard M. Carlton	NIH297.1C1C1C1	4747

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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
SNYDER, STUART	

ART UNIT	PAPER NUMBER
1648	

NOTIFICATION DATE	DELIVERY MODE
05/04/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/659,698	CARLTON ET AL.	
	Examiner	Art Unit	
	Stuart W. Snyder	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-19 and 23-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-19 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/5/2006*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 15-17, 19 and 23-25 are subject to examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 15-17, 19 and 23-25 stand rejected under 35 USC § 112, 1st ¶ as failing to meet the enablement requirement. The position of record of the Office is summarized as follows:

   1) The critical properties of the claimed invention are that the PEGylated bacteriophage possess a 15% longer half-life than corresponding wild-type phage—line 7, page 15 of applicants' specification define "a physico-chemically altered phage, as used herein, has a half-life within the animal that is at least 15% greater that the half-life of the original unmodified phage from which it was derived" and that PEGylated bacteriophage evade a host defense system relative to wild-type bacteriophage,
   2) Prior art does not teach methods of PEGylating bacteriophage so that the phage possess the critical properties,
   3) There are no working examples of the claimed invention in the specification as filed nor in Applicants' post-filing publications,

4) The guidance in the specification is insufficient to successfully PEGylate bacteriophage, maintain infectivity, and increase circulating half-life by evading the host defense system,
5) The art is unpredictable, and
6) The amount of experimentation to produce PEGylated bacteriophage possessing 15% longer half-life by evading the host defense system than corresponding wild-type phage would be great.

Applicants have responded by initially reciting Dr. Merril's long and distinguished career accomplishments, attesting that all of the proposed techniques used in subsequent work in this area were available at the time of filing, and that others have, subsequent to filing, used some of the methods taught in the specification or otherwise available at the time of filing to:

1) Prepare a PEGylated adenovirus preparation, and
2) Prepare antibodies against phage tail proteins.

The Office does not dispute anything in the preceding paragraph. This Examiner, however, does not see any evidence of working examples of the claimed invention by Applicants or others that embody the claimed invention during the 13 years that have followed Applicants' conception of the claimed invention.

3. Regarding the various arguments recently presented:

1) Applicant provides evidence that monoclonal antibodies have been created against phage tail proteins and asserts that such techniques are useful to protect phage tail during subsequent PEGylation procedures. The Office does

not dispute the evidence of monoclonal antibody production specific to phage tail proteins. However, there is no evidence provided that the assertation of the usefulness of antibody protection is, in fact, true. The DeHaard, et al. reference specifically teaches that tail protein-specific antibodies can be generated that prevent infection by interfering with the attachment of the phages to host cells. The reference does not teach subsequent chemical modification and therefore is silent to the critical issue of whether or not such antibody binding will protect phage from inactivation upon PEGylation. Thus, the DeHaard, et al. reference is irrelevant to the question of whether or not antibodies are capable of protection of phage tail from inactivation during PEGylation and does not support an enabling disclosure by applicant.

2) Applicant reviews the O'Riordan et al. reference and interprets Figure 5 as a time course experiment supporting the central claim of the present application. The Examiner agrees that data is presented in Figure 5 of O'Riordan, et al. compares wild-type virus with PEGylated virus after a period of 3 days. However, the experiments of O'Riordan, et al. do not constitute time course experiments necessary to calculate half-lives of virions. Applicants' specification describes at least one method of determining the half-life of circulating bacteriophage in mice (see example 3, page 29-30):

   a. Inject two groups of mice with 10^{12} modified or unmodified phage per mouse,

   b. Bleed mice at regular intervals,

c. Assay blood samples for phage content using pfu assays, and

d. Determine the half-life of circulating phage for each group of mice.

The experiments conducted by O'Riordan, et al. differ from the protocol in several important respects:

a. Mice were injected with $2.5x10^{10}$ virions per mouse,

b. Mice were not bled to sample for virus but rather virus was obtained from lungs and furthermore virus concentration was determined at only one time point—three days,

c. Virus concentration was determined by β-Gal assays not pfu assays (the Examiner recognizes that pfu assays for the adenovirus construct of O'Riordan, et al. is not possible because the virus is replication deficient), and

d. Viral half-life was not determined.

The significance of the differences between Applicants' proposed experiments and O'Riordan,et al.'s actual experiments is:

a. It is well-known that the amount of input virus is important in neutralization experiments—higher input virus leads to lower apparent neutralization titers—and thus may bias apparent circulating half-life determinations,

b. Lung concentration of virus may be indicative of circulating virus concentration but no correlation was established—the claimed invention is directed to circulating virus,

c. O'Riordan, et al. measured the amount of virus that infected the lungs not the amount of virus that remains circulating and therefore capable of infecting additional targets—conceivably, O'Riordan, et al. measured a difference in the infectivity between treated and untreated virus in the lung rather than the circulating properties of the different viral preparations, and

d. Insufficient data was collected by O'Riordan, et al. to calculate half-lives.

Thus, O'Riordan, et al. teaches that a mammalian virus vector may be modified and retain infectivity relative to untreated virus vectors. However, O'Riordan, et al. does not teach that tailed bacteriophage can be PEGylated, retain infectivity or possess increased half-lives, the critical property of the claimed invention. Therefore, O'Riordan, et al. does not support enablement of Applicants' disclosure by teaching increased half-life of adenovirus after PEGylation.

3) Regarding the method of activating PEG and subsequently modifying the phage:

The Examiner previously and erroneously asserted that O'Riordan, et al. teaches that Applicants' preferred method of activating and using activated PEG to modify adenovirus reduces the infectivity of the virus; Applicants' preferred method is succinimidyl carbonate whereas O'Riordan, et al. teaches succinimidyl succinate. However, the chemistry of succinimidyl succinate and

succinimidyl carbonate in activating PEG is the similar. Therefore, one would expect from the limited data submitted by Applicants and otherwise published, that use of Applicants' preferred method of activating PEG and PEGylating phage would result in reduced infectivity. Therefore, O'Riordan, et al. does not support enablement of Applicants' disclosure by teaching a method of PEGylation demonstrably contemplated by Applicants. O'Riordan, et al. does support the Examiners' position that the art is unpredictable.

4. Regarding a central aspect of claimed invention, delayed inactivation of PEGylated bacteriophage **by an animal's host defense system** relative to unmodified virus: The specification and post-filing literature are silent. Demonstration of such a mechanism of prolonged in vivo bacteriophage circulation would involve experiments such as: Differential B-cell or T-cell responses, differential complement activation, differential "clear[ing] out of the blood stream ...by the organs of the reticulo-endothelial system, such as the spleen, liver and bone marrow"—the type of experiment that Dr. Merril previously performed to discover the fate of circulating bacteriophage (Geier, et al.)—and the like. Thus there are no working examples in the specification or subsequent filing to suggest that PEGylated bacteriophage would differentially be inactivated by an animals host defense system relative to unmodified bacteriophage. Another plausible mechanism for the increased lung infectivity of PEGylated adenovirus, the sole example of successful viral PEGylation, is that the virus is simply more stable after PEGylation. It is well known that viruses are differentially

labile, in vivo and in vitro. Whereas HIV has a inactivation half-life of approximately ½ h, orthopox and other virus' half-lifes are considerably longer. PEGylation may structually stabilize viruses and increase the circulating half-life and/or infectivity.

5. Applicants' arguments have been duly considered and found unconvincing for reasons of record and those presented herein. Rejection of claims 15-17, 19 and 23-25 under 35 USC § 112, 1st ¶ as failing to be enabled by the disclosure is maintained.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart W. Snyder whose telephone number is (571) 272-9945. The examiner can normally be reached on 9:00 AM-5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stuart W Snyder
Examiner
Art Unit 1648

SWS

BRUCE R. CAMPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600